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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte
JOSEPH ROBERTS and NATARAJAN SETHURAMAN

Appeal 2007-3933[1]
Application 09/972,245
Technology Center 1600

DECIDED: March 26, 2008

Before TONI R. SCHEINER, ERIC GRIMES, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

Opinion for the Board filed by *Administrative Patent Judge* TONI R. SCHEINER

Opinion Dissenting filed by *Administrative Patent Judge* JEFFREY N. FREDMAN

SCHEINER, *Administrative Patent Judge*

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[1] Heard February 12, 2008.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1-13, 17-22, and 41-46.[2] The claims stand rejected as anticipated by and obvious over the prior art. We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

BACKGROUND

"When a host encounters a foreign agent in its circulation, the host's immune system may initiate an immune response. This response includes the production of agent-inactivating antibodies that also enable the reticuloendothelial system to clear the agent from circulation" (Spec. 1: 7-9).

"One strategy for protecting these agents is to covalently modify them with agents like carbohydrates or biocompatible polymers, like Polyethylene Glycol ('PEG')" (Spec. 1: 15-16). "PEGylation increases the stability of proteins . . . and also greatly reduces their antigenicity (measured by the extent of reaction of antibodies raised against unmodified protein to PEGylated protein) and immunogenicity (measured by the extent of antibody formation against PEGylated protein in treated animals), as measured by *in vitro* immunological techniques" (Spec. 1: 19 to 2: 1).

One drawback of this protection is that "PEGylation often reduces the biological activity of the agent. The extent of reduction varies with the type of activated PEG used and the number of Polyethylene Glycol moieties attached to the agent. The biological activity also is affected by the extent to which an agent is modified with a particular PEG" (Spec. 2: 3-7).

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[2] Claims 14-16 and 23-40 are also pending, but have been withdrawn from consideration.

According to Appellants, choosing modification conditions for a given therapeutic agent (i.e., the type of activated PEG to use, and the extent of modification) based only on the criteria of initial "acceptable loss of therapeutic activity . . . and the reduction of antigenicity and immunogenicity of the agent" (Spec. 2: 8-11) "often leads to an arbitrary result" (Spec. 1: 12-13), and is "insufficient . . . where such agents are administered . . . over a prolonged period of time" (Spec. 2: 17-19).

According to Appellants, this is "because none of the foregoing criteria take into consideration the effect of the host's response on the agent's biological activity *after* the PEGylated agent is administered to the host" (Spec. 2: 19-21). "[O]ver-PEGylation of an agent, as well as over-modification of an agent with any modifying agent, can disrupt the secondary and/or tertiary structure of the agent, thus exposing new antigenic determinants to the immune system" (Spec. 3: 4-6). Administration of a modified agent over a long period of time can also induce "detoxifying mechanisms that serve to convert the therapeutic agent to a therapeutically inactive compound" (Spec. 5: 9-10).

According to Appellants, measuring the loss of therapeutic activity of the modified agent *before* it is administered to a patient is not relevant to predicting subsequent host-mediated loss of activity (Spec. 2: 8 to 3:8). Nor is the extent of antibody formation against the modified agent (i.e., antigenicity and immunogenicity) "predictive of clearance of activity" (Spec. 27: 4). Thus, "reliance on only the aforementioned criteria will produce an agent that is not optimally protected from the host's immune system, or otherwise from *in situ* inactivation" (Spec. 2: 21-23).

"An ideal level of modification is that which yields the smallest decrease in biological activity between doses" (Spec. 21: 14-15). The Specification describes "a direct *in vivo* functional method of ascertaining [ideal] modification conditions of a therapeutic agent that allow the agent to evade the host's self-defense mechanisms and consequently extend the effective therapeutic life of the therapeutic agent in the host" (Spec. 5: 12-15).

STATEMENT OF THE CASE

"The basic inventive method entails administering a modified therapeutic agent . . . to a subject. Next, the blood of the subject is assayed for biological activity of the therapeutic. The subject is then treated with one or more doses of the modified agent . . . at levels useful in therapy. The blood of the subject is assayed again for biological activity of the therapeutic agent . . . Any decrease in activity from the first measurement and subsequent measurements is ascertained. The foregoing may be repeated multiple times. The method may also be repeated with different lots of therapeutic agent, which differ in the extent of modification. An ideal level of modification is that which yields the smallest decrease in biological activity between doses." (Spec. 21: 7-15.)

Claim 1 is representative, and reads as follows:

1. A method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer, comprising:

(a) assaying a biological activity of a first modified therapeutic agent after said first modified therapeutic agent has been administered to a subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(b) assaying the biological activity of said first modified therapeutic agent after at least one booster dose of said first modified therapeutic agent has been administered to said subject;

(c) assaying the biological activity of a second modified therapeutic agent after said second modified therapeutic agent has been administered to a subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(d) assaying the biological activity of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said subject; and

(e) comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer.

The claims stand rejected as follows:

1. Claims 1-3, 7, 9, 10, 17, 18, 41, 42, and 44 under 35 U.S.C. § 102(b) as anticipated by Chinol.[3]

2. Claims 1-3, 7, 9, 10, 17, 18, 41, 42, and 44 under 35 U.S.C. § 102(a) as anticipated by Deckert.[4]

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[3] M. Chinol et al., *Biochemical Modifications of Avidin Improve Pharmacokinetics and Biodistribution, and Reduce Immunogenicity*, 78(2) British Journal of Cancer 189-197 (1998).

[4] P.M. Deckert et al., *Pharmacokinetics and Microdistribution of Polyethylene Glycol-Modified Humanized A33 Antibody Targeting Colon Cancer Xenografts*, 87 Int. J. Cancer 382-390 (2000).

3. Claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41-46 under 35 U.S.C. § 103(a) as unpatentable over Alvarez[5] in view of Graham[6] and Francis.[7]

4. Claim 4 under 35 U.S.C. § 103(a) as unpatentable over Alvarez, Graham and Francis, in view of Pedersen.[8]

5. Claims 8, 11, and 20-22 under 35 U.S.C. § 103(a) as unpatentable over Alvarez, Graham and Francis, in view of Roberts.[9]

6. Claims 18 and 19 under 35 U.S.C. § 103(a) as unpatentable over Alvarez, Graham and Francis, in view of Bollin.[10]

ISSUE ON APPEAL

There are six separate rejections of the claims, but the scope of the limitation "assaying a biological activity of a . . . modified therapeutic agent" is central to each rejection, and Appellants' arguments are primarily directed to that limitation.

Essentially, Appellants contend the Examiner's "assertion that . . . measurement of 'antigenicity' or 'immunogenicity' of a therapeutic agent

[5] O.A. Alvarez & G. Zimmerman, *Pegaspargase-Induced Pancreatitis*, 34 Medical and Pediatric Oncology 200-205 (2000).
[6] M.L. Graham et al., *Toxicity, Pharmacology and Feasibility of Administration of PEG-L-Asparaginase as Consolidation Therapy in Patients Undergoing Bone Marrow Transplantation for Acute Lymphoblastic Leukemia*, 21 Bone Marrow Transplantation 879-885 (1998).
[7] G.E. Francis et al., *PEGylation of Cytokines and Other Therapeutic Proteins and Peptides: the Importance of Biological Optimisation of Coupling Techniques*, 68 International Journal of Hematology 1-18 (1998).
[8] U.S. Patent 6,531,122 B1 to Pedersen et al., issued March 11, 2003.
[9] J. Roberts & W.G. McGregor, *Inhibition of Mouse Retroviral Disease by Bioactive Glutamase-Asparaginase*, 72 Journal of General Virology 299-305 (1991).
[10] U.S. Patent 4,678,812 to Bollin et al., issued July 7, 1987.

constitutes 'assaying a biological activity' of the therapeutic agent . . . is factually and legally erroneous" (Reply Br. 1).

The Examiner, on the other hand, argues "it is reasonable to interpret 'biological activity' to embrace antigenicity" because the Specification expressly "states 'biological activity' means any cellular or physiological response or reaction that the agent causes, either directly or indirectly, and that the biological activity is not necessarily the same activity as the therapeutic benefit that the agent bestows upon the subject" (Ans. 12).

"It is axiomatic that, in proceedings before the PTO, claims in an application are to be given their broadest reasonable interpretation *consistent with the specification*." *In re Sneed*, 710 F.2d 1544, 1548 (Fed. Cir. 1983) (emphasis added).

Thus, the principal issue raised by this appeal - with respect to the anticipation rejections and the obviousness rejections - is whether "antigenicity" and "immunogenicity" are encompassed by the broadest reasonable interpretation of "biological activity," when those terms are interpreted in light of Appellants' Specification.

FINDINGS OF FACT[11]

1. According to the Specification, "the term 'modified therapeutic agent' means a therapeutic agent wherein a modifying agent has been linked or joined to the therapeutic agent. By modifying agent, it is meant an agent or

[11] Abbreviated "FF".

compound that reduces the immunogenic or antigenic response of the subject towards the therapeutic agent, compared to the immunogenic or antigenic response of the subject towards the same therapeutic agent that has not been modified" (Spec. 14: 8-12).

2. According to the Specification, assaying the "biological activity" of a modified agent means assaying "a cellular or physiological response or reaction that the agent causes, either directly or indirectly. The biological activity can be assessed *in vivo*, *in vitro*, or *in situ*. Examples of biological activity include, but are not limited to, an enzyme catalyzing a reaction, a molecule binding a receptor or antibody, mediating a receptor-mediated response such as ion influx/efflux or generation of second messengers, antagonizing or blocking a receptor-mediated response, induction of apoptosis and release or uptake of a neurotransmitter or hormone. The biological activity is not necessarily the same activity as the therapeutic benefit that the agent bestows upon the subject" (Spec. 13: 6-13).

3. According to the Specification, the "antigenicity" of a modified agent, for example, a PEGylated protein, is "measured by the extent of reaction of antibodies raised against unmodified protein to PEGylated protein" (Spec. 1: 21-22). In other words, as defined by the Specification, the antigenicity of a modified agent is a measure of the extent to which antibodies raised against the agent cross-react with the modified agent.

4. According to the Specification, the "immunogenicity" of a modified protein is "measured by the extent of antibody formation against PEGylated protein in treated animals" (Spec. 1: 23 to 2: 1). That is, as defined by the Specification, the immunogenicity of a modified agent is a measure of the

extent to which the modified agent elicits antibodies to itself in a treated animal.

5. Example 3 of the Specification demonstrates that the immunogenicity of a modified agent (in this case, various forms of PEGylated *Pseudomonas 7A* Glutaminase-Asparaginase (PGA)), is not predictive of the agent's ability to maintain its activity (in this case, enzyme activity) *in vivo*. For example, "ELISA results showed that despite detectable levels of antibody in the serum, some preparations of PEG-PGA . . . were able to maintain enzyme activity in the serum at the usual half-life levels. However, some ALD [aldehyde]-PGA preparations showed no detectable antibody development on ELISA, even though the enzyme had been successfully cleared from the serum" (Spec. 26: 17-21; Table 1).

6. According to Appellants, "ELISA is not predictive of clearance of activity, . . . [thus] the glutaminase assay (or relevant biological activity for other agents) must be performed on serum to determine the success of different PEGylation strategies" (Spec. 27: 4-6).

7. The Specification expressly defines the terms "antigenicity" and "immunogenicity" (FF 3, 4) and states that "[t]he existing criteria (antigenicity, immunogenicity and acceptable loss of therapeutic activity) for determining the activated PEG used and the extent of PEGylation are insufficient . . . in instances where such agents are administered . . . over a prolonged period of time" (Spec. 2: 16-19), in contrast to measuring "the agent's biological activity *after* the PEGylated agent is administered to the host" (Spec. 2: 20-21). Thus, the Specification implicitly excludes measuring a modified agent's antigenicity and/or immunogenicity from measuring its

biological activity. That is, when read in the context of the Specification as a whole, the broadest reasonable interpretation of the term "biological activity" does not embrace the terms "antigenicity" or "immunogenicity" (as they are defined in the Specification).

Chinol

8. Chinol describes modifying avidin "by covalently linking PEG via its amino groups at different molar ratios" (Chinol 189, col. 2).

9. Chinol describes evaluating the loss of bioactivity (i.e., biological activity, in this case, biotin binding) due to PEGylation, using an ELISA assay (Chinol 195, col. 1). "[I]ncreasing the number of [PEG] chains bound per molecule of [avidin] . . . progressively decreased the in vitro biotin binding evaluated by [the] ELISA assay" (Chinol 195, col. 1; Table 2). Biotin binding activity in the sera of treated mice was not evaluated.

10. Chinol describes evaluating the immunogenicity and antigenicity (as those terms are defined in the present Specification) of the PEGylated avidins as follows: "In order to evaluate immunogenicity . . . mice were injected . . . with modified [avidins]. Antibody response against the homologous immunogen, evaluated by ELISA, became detectable in the majority of tested animals after two . . . or three injections . . . and rose to a high titre after a further boost" (Chinol 194, col. 1). "The cross-reactivity of modified vs native [avidin] was also evaluated by testing the reactivity of . . . pooled antinative [avidin] sera . . . and of an anti-[avidin] monoclonal antibody . . . on microtitre plates coated with different modified [avidins]" (Chinol 194, col. 1).

11. Thus, Chinol describes optimizing the PEGylation of avidin based on acceptable loss of biological activity, immunogenicity, and antigenicity.

Deckert

12. Deckert describes optimizing PEGylation of humanized A33 antibody (huA33) based on "the highest PEG:Ab ratio for each PEG size that would not diminish antibody binding by more than 50% as determined by mixed hemadsorption assay on A33-antigen-positive SW1222 colon cancer cells" (Deckert 383, col. 2, and 384, col. 2).

13. Deckert describes evaluating the immunogenicity (as that term is defined in the present Specification) of PEGylated huA33 (Deckert 383, col. 2).

14. Thus, Deckert describes optimizing the PEGylation of huA33 based on acceptable loss of biological activity (in this case, the ability of PEGylated huA33 to bind A33 in vitro) and immunogenicity.

Alvarez

15. Alvarez describes the possible higher incidence of pancreatitis associated with Oncaspar® (polyethylene glycol-L-asparaginase, also known as pegaspargase or PEG-Asp) as compared with unmodified L-asparaginase (Alvarez 201-204). Oncaspar® was not compared with any other form of modified L-asparaginase.

Graham

16. Graham describes a clinical trial to evaluate the toxicity of PEG-L-asparaginase (PEG-L-A), manifested as nausea, vomiting, and pancreatitis, in patients undergoing bone marrow transplantation for acute lymphoblastic

leukemia (Graham 880-881). PEG-L-A was not compared with any other form of asparaginase.

17. The immunogenicity (as defined in the present Specification) of PEG-L-asparaginase was evaluated (Graham 881).

Francis

18. Francis discusses "the importance of biological optimisation of every step in the PEGylation procedure in order to achieve good conservation of bioactivity" (Francis 14, col. 2).

19. The optimisation procedure described by Francis does not include evaluating the bioactivity of a PEGylated agent after administration *in vivo*.

DISCUSSION

Anticipation by Chinol

Claims 1-3, 7, 9, 10, 17, 18, 41, 42, and 44 stand rejected under 35 U.S.C. § 102(b) as anticipated by Chinol.

According to the Examiner, Chinol describes administering multiple doses of various PEGylated avidins to subjects and testing their sera "for anti-avidin reactivity by ELISA" (Ans. 4). The Examiner contends that "[a]nti-avidin reactivity is a measure of the antigenicity of the modified avidins, which in turn is considered to be a biological activity as recited in the claims" (Ans. 4). "Thus Chinol anticipates the claims" (Ans. 4).

Appellants contend that Chinol "used ELISA to determine the titer of antibodies produced against avidin or [PEG] modified avidin" as a measure of "the immunogenicity of the protein" (App. Br. 10), rather than measuring "the biological activity [of the modified avidin] in circulation" (*id.*), "as a guide to determining the desired extent of modification" (App. Br. 11).

Appellants contend that the Examiner is incorrect in asserting that "measurement of 'antigenicity' or 'immunogenicity' of a therapeutic agent constitutes 'assaying a biological activity' of the therapeutic agent" (Reply Br. 1). Therefore, "Chinol fails to disclose 'comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent" as recited in claim 1" (App. Br. 10).

Essentially, the Examiner and Appellants agree that Chinol measures and compares the "immunogenicity" and/or "antigenicity" (as those terms are defined in the present Specification) of various forms of PEGylated avidin after administration of booster doses of the modified agents, but disagree as to whether immunogenicity and antigenicity are encompassed by the term "biological activity" when those terms are interpreted based on the Specification.

We agree with Appellants that the broadest reasonable interpretation of the term "biological activity" does not embrace the terms "antigenicity" or "immunogenicity," when those terms are read in context, given the fact that the Specification expressly defines the terms "antigenicity" and "immunogenicity" (FF 3, 4), and states that the existing criteria for optimizing modification of therapeutic agents, i.e., "antigenicity, immunogenicity and acceptable loss of therapeutic activity" (Spec. 2: 16) produce arbitrary results (Spec. 2: 12-13), in contrast to measuring "the agent's biological activity *after* the PEGylated agent is administered to the host" (Spec. 2:20-21) (FF 7).

We find that Chinol does not measure the biological activity of PEGylated avidin after administration of initial and booster doses, and therefore, does not anticipate the claimed invention.

The rejection of claims 1-3, 7, 9, 10, 17, 18, 41, 42, and 44 under 35 U.S.C. § 102(b) as anticipated by Chinol is reversed.

Anticipation by Deckert

Claims 1-3, 7, 9, 10, 17, 18, 41, 42, and 44 stand rejected under 35 U.S.C. § 102(a) as anticipated by Deckert.

According to the Examiner, Deckert teaches "a method in which differently pegylated antibodies are administered to subjects, followed by booster doses, and measures of antigenicity" (Ans. 5). "Thus Deckert anticipates the claims" (Ans. 5).

Appellants contend that the Examiner is incorrect in asserting that "measurement of 'antigenicity' or 'immunogenicity' of a therapeutic agent constitutes 'assaying a biological activity' of the therapeutic agent" (Reply Br. 1). Therefore, "Deckert fails to disclose 'comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent" as recited in claim 1" (App. Br. 12). According to Appellants, Deckert "also fails to disclose assaying a first or second modified therapeutic agent after the first or second modified therapeutic agent 'has been administered to a subject'" (App. Br. 12), and "the extent of PEGylation was determined solely on acceptable loss of biological activity without the use of in vivo studies" (*id.*).

Essentially, the Examiner and Appellants agree that Deckert measures and compares the "immunogenicity" and/or "antigenicity" (as those terms

are defined in the present Specification) of various forms of PEGylated avidin after booster doses of the modified agents, but disagree as to whether immunogenicity and antigenicity are encompassed by the term "biological activity" when those terms are interpreted based on the Specification.

Again, we agree with Appellants that the broadest reasonable interpretation of the term "biological activity" does not embrace the terms "antigenicity" or "immunogenicity," when those terms are read in context, given the fact that the Specification expressly defines the terms "antigenicity" and "immunogenicity" (FF 3, 4), and states that the existing criteria for optimizing modification of therapeutic agents, i.e., "antigenicity, immunogenicity and acceptable loss of therapeutic activity" (Spec. 2: 16) produce arbitrary results (Spec. 2: 12-13), in contrast to measuring "the agent's biological activity *after* the PEGylated agent is administered to the host" (Spec. 2:20-21) (FF 7).

We find that Deckert does not measure the biological activity of PEGylated avidin after administration of initial and booster doses, and therefore, does not anticipate the claimed invention.

The rejection of claims 1-3, 7, 9, 10, 17, 18, 41, 42, and 44 stand under 35 U.S.C. § 102(a) as anticipated by Deckert is reversed.

Obviousness based on Alvarez, Graham, and Francis

Claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41-46 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Alvarez in view of Graham and Francis.

Both Alvarez and Graham are directed to studies to evaluate toxicity of PEGylated L-asparaginase, manifested as nausea, vomiting and

pancreatitis (FF 15, 16). The Examiner contends that "relapse" and "evaluations of toxicity are . . . considered to be measurements of biological activity" (Ans. 6), but such an interpretation of the terms relapse and toxicity is not consistent with the Specification's teaching that "[a]n ideal level of modification is that which yields the smallest decrease in biological activity between doses" (Spec. 21: 14-15). Clearly, one would not consider a modification that yields the smallest decrease in relapse or toxicity between doses to be ideal, thus it is not reasonable to interpret "toxicity" and "relapse" as "biological activity," as that term is used in the Specification.

In any case, neither Alvarez nor Graham is directed to an assay to determine the optimal strategy for modifying therapeutic agents, and neither compares different forms of modified therapeutic agents under any criteria (FF 15, 16, 17).

Francis, on the other hand, *is* directed to methods for determining the optimal strategy for PEGylating therapeutic agents, but does not describe a method that includes evaluating the biological activity (as that term is used in the present Specification (FF 7)) of PEGylated agents after administration *in vivo* (FF 18, 19).

We find that the Examiner has not established an adequate factual basis to support his conclusion that "[i]t would have been obvious to one of ordinary skill in the art to produce a variety of differently pegylated versions of asparaginase, . . . compare them in head to head studies in vivo . . . [and] measure the effects of the drugs after each injection, as patients undergoing treatment for ALL, such as those in the Graham and Alvarez studies, are continuously monitored for disease progress" (Ans. 7).

The rejection of claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41-46 under 35 U.S.C. § 103(a) as unpatentable over Alvarez in view of Graham and Francis is reversed.

Additional Obviousness Rejections Based on Alvarez, Graham, and Francis

Claim 4 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Alvarez, Graham and Francis, in view of Pedersen.

Claims 8, 11, and 20-22 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Alvarez, Graham and Francis, in view of Roberts.

Claims 18 and 19 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Alvarez, Graham and Francis, in view of Bollin.

We find that Pedersen, Roberts, and Bollin do not cure the underlying deficiency in the Examiner's proposed combination of Alvarez, Graham, and Francis, and these latter three rejections of claims 4, 8, 11, and 18-22 under 35 U.S.C. § 103(a) are reversed as well.

SUMMARY

The rejection of claims 1-3, 7, 9, 10, 17, 18, 41, 42, and 44 under 35 U.S.C. 102(b) as anticipated by Chinol is reversed.

The rejection of claims 1-3, 7, 9, 10, 17, 18, 41, 42, and 44 under 35 U.S.C. § 102(a) as anticipated by Deckert is reversed.

The rejection of claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41-46 under 35 U.S.C. § 103(a) as unpatentable over Alvarez in view of Graham and Francis is reversed.

The rejection of claim 4 under 35 U.S.C. § 103(a) as unpatentable over Alvarez, Graham and Francis, in view of Pedersen is reversed.

The rejection of claims 8, 11, and 20-22 under 35 U.S.C. § 103(a) as unpatentable over Alvarez, Graham and Francis, in view of Roberts is reversed.

The rejection of claims 18 and 19 under 35 U.S.C. § 103(a) as unpatentable over Alvarez, Graham and Francis, in view of Bollin is reversed.

REVERSED

Dissenting Opinion by FREDMAN, *Administrative Patent Judge*.

I respectfully dissent. I would affirm the Examiner's anticipation and obviousness rejections, based upon the Examiner's reasoning and the following comments.

I think that the majority has arrived at an incorrect result in this case based upon narrowly interpreting the limitation "biological activity" in a manner that is inconsistent with the express definition of "biological activity" in the Specification consistent with the broadest reasonable interpretation in light of the Specification.

The majority reverses the Chinol anticipation rejection, based upon Appellants' Specification teaching that "existing criteria for optimizing modification of therapeutic agents, i.e., 'antigenicity, immunogenicity and acceptable loss of therapeutic activity' (Spec. 2: 16) produce arbitrary results (Spec. 2: 12-13), in contrast to measuring 'the agent's biological activity *after* the PEGylated agent is administered to the host'(Spec. 2: 20-21) (FF 7)" (Supra 13-14). I think that this argument mischaracterizes what Chinol (and the other cited references) must teach.

"The law of anticipation does not require that the reference 'teach' what the subject [application] teaches. Assuming that a reference is properly 'prior art,' it is only necessary that the claims under attack . . . 'read on' something disclosed in the reference, i.e., all limitations of the claim are found in the reference." *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 772 (Fed. Cir. 1983). In the current case, Appellant acknowledges that "[a]ll of the pending rejections hinge upon the examiner's assertion that the cited prior art's measurement of "antigenicity" or "immunogenicity" of a

therapeutic agent constitutes "assaying a biological activity" of the therapeutic agent" (Rep. Br. 1).

It is black letter law that "the PTO gives a disputed claim term its broadest reasonable interpretation during patent prosecution". *In re Bigio*, 381 F.3d 1320, 1324 (Fed. Cir. 2004). The court recognizes the fairness of reading claims broadly "before a patent is granted [since] the claims are readily amended as part of the examination process." *Burlington Indus. v. Quigg*, 822 F.2d 1581, 1583 (Fed. Cir. 1987). "Thus, a patent applicant has the opportunity and responsibility to remove any ambiguity in claim term meaning by amending the application". *Bigio*, 381 F.3d at 1324. Applying the broadest reasonable interpretation to claims also "serves the public interest by reducing the possibility that claims, finally allowed, will be given broader scope than is justified." *In re Am. Acad. of Sci. Tech. Ctr.,* 367 F.3d 1359, 1364 (Fed.Cir.2004).

In this case, there is an express definition of "biological activity" in the Specification: "The methods as provided in the current invention involve ascertaining the modification conditions of a therapeutic agent, by assessing the biological activity of the modified agent, after administration to an animal or subject. By 'biological activity' is meant a cellular or physiological response or reaction that that agent causes, either directly or indirectly" (Spec. 13:4-7).

This express definition of "biological activity" clearly includes measurement of "antigenicity" or "immunogenicity" as in Chinol since it is admitted and unquestionable that both "antigenicity" and "immunogenicity"

cause physiological responses and reactions, directly and indirectly, as required by the Specification (*see, e.g.,* FF 3-4).

The Federal Circuit in *Trans Texas Holdings* affirmed a USPTO obviousness rejection in a fact pattern that is legally indistinguishable from the instant situation. In *Trans Texas Holdings*, the issue was whether the phrase "responsive to the rate of inflation" should be interpreted in a limiting fashion based upon the examples in that Specification or broadly interpreted since "the specification's definition only requires that the inflation adjustment be "directly responsive" to a market indicator of inflation." *In re Trans Texas Holdings Corp.*, 498 F.3d 1290, 1298 (Fed. Cir. 2007). The issue revolved around whether narrow examples in the Specification controlled over a broad express definition. *Id.* at 1298. The court found, consistent with the black letter law cited above, that "it is improper to 'confin[e] the claims to th[e] embodiments' found in the specification." *Id.* at 1299. The court affirmed the rejection when the properly broad claim construction was applied. *Id.* at 1299.

I contend that the majority's reliance on the examples and data in the Specification to define "biological activity" serves to confine the claims to embodiments found in the Specification. This narrow reading is in clear contrast with what I perceive to be guidance for the "broadest reasonable interpretation rule" given by the Federal Circuit, as particularly shown in *Trans Texas Holdings*, and found in many other decisions as well. Reading the claims with the "broadest reasonable interpretation" supports, in my view, the interpretation of the Examiner. I would therefore affirm the

Examiners anticipation and obviousness rejections, which all depend upon the broad interpretation. For these reasons, I respectfully dissent.

lp

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